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Smoking Status, Nicotine Medication, Vaccination, and COVID-19 Hospital Outcomes: Findings from the COVID EHR Cohort at the University of Wisconsin (CEC-UW) Study

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Abstract

Introduction: Available evidence is mixed concerning associations between smoking status and COVID-19 clinical outcomes. Effects of nicotine replacement therapy (NRT) and vaccination status on COVID-19 outcomes in smokers are unknown.

Methods: Electronic health record data from 104 590 COVID-19 patients hospitalized February 1, 2020 to September 30, 2021 in 21 U.S. health systems were analyzed to assess associations of smoking status, in-hospital NRT prescription, and vaccination status with in-hospital death and ICU admission.

Results: Current (n = 7764) and never smokers (n = 57 454) did not differ on outcomes after adjustment for age, sex, race, ethnicity, insurance, body mass index, and comorbidities. Former (vs never) smokers (n = 33 101) had higher adjusted odds of death (aOR, 1.11; 95% CI, 1.06–1.17) and ICU admission (aOR, 1.07; 95% CI, 1.04–1.11). Among current smokers, NRT prescription was associated with reduced mortality (aOR, 0.64; 95% CI, 0.50–0.82). Vaccination effects were significantly moderated by smoking status; vaccination was more strongly associated with reduced mortality among current (aOR, 0.29; 95% CI, 0.16–0.66) and former smokers (aOR, 0.47; 95% CI, 0.39–0.57) than for never smokers (aOR, 0.67; 95% CI, 0.57, 0.79). Vaccination was associated with reduced ICU admission more strongly among former (aOR, 0.74; 95% CI, 0.66–0.83) than never smokers (aOR, 0.87; 95% CI, 0.79–0.97).

Conclusions: Former but not current smokers hospitalized with COVID-19 are at higher risk for severe outcomes. SARS-CoV-2 vaccination is associated with better hospital outcomes in COVID-19 patients, especially current and former smokers. NRT during COVID-19 hospitalization may reduce mortality for current smokers.

Implications: Prior findings regarding associations between smoking and severe COVID-19 disease outcomes have been inconsistent. This large cohort study suggests potential beneficial effects of nicotine replacement therapy on COVID-19 outcomes in current smokers and outsized benefits of SARS-CoV-2 vaccination in current and former smokers. Such findings may influence clinical practice and prevention efforts and motivate additional research that explores mechanisms for these effects.

Introduction

As of June 2022, the COVID-19 outbreak has resulted in more than 85 million cases and over 1 million deaths in the United States.[1] Because smoking increases risk for respiratory infection, induces inflammatory responses, and impairs pulmonary immune function,[2,3] smoking has been hypothesized to be a major risk factor for COVID-19 infection and progression.[4,5] In addition, the SARS-CoV-2 virus enters the host cell by binding to the angiotensin-converting enzyme 2 (ACE2) receptor,[6] which may be upregulated in smokers' upper airways,[7–9] and perhaps produce greater viral loads and more severe COVID-19.

Surprisingly, early observational studies indicated that the prevalence of smoking among COVID-19 patients was substantially lower than in the general population.[10,11] Some suggested that nicotine might confer a paradoxical protection from COVID-19 and that medicinal nicotine might reduce the likelihood of COVID-19 infection and its severity[10,12–14]; others have attributed the smoking prevalence observations to bias and confounding.[15–17]

Large-scale cohort studies and research syntheses indicate that, compared with never smokers, former smokers infected with SARS-CoV-2 are at increased risk for progression to more severe disease and death.[11,18,19] Evidence linking current (vs. never) smoking with severe COVID-19 has been less conclusive.[11,18,20–22]

Available meta-analyses have typically synthesized unadjusted associations between smoking status and COVID-19 severity. However, when analyses are statistically adjusted for medical comorbidities, associations between current and former smoking and COVID-19 disease severity are reduced or eliminated.[18,23] In addition, some studies have not differentiated some smoking status groups: collapsing across former and never smokers[24,25] or collapsing across current and former smokers.[20,26] Other studies have not included missing data[27] or have imputed missings as never smokers.[18,28] Importantly, missing smoking status has been found to be a significant predictor of hospital admission and critical COVID-19 illness.[29,30]

The production of safe and efficacious COVID-19 vaccines has been a pivotal public health achievement, but whether vaccination benefit varies with smoking status is unknown. Compared with nonsmokers, current and former smokers have more negative attitudes towards vaccines in general and report greater hesitancy to accept COVID-19 vaccination.[31] Moreover, some evidence indicates that immunological responses to COVID-19 vaccines are diminished and decline more rapidly in current smokers compared to nonsmokers.[32]

This study examines associations of smoking status with mortality and ICU admission in a large cohort study using electronic health record (EHR) data from all COVID-19 hospitalized patients admitted at 21 US health systems. Smoking status categories (never, current, former, and missing) were used to predict COVID-19 outcomes with and without statistical adjustment for age, sex, race, ethnicity, body mass index (BMI), insurance status, and medical comorbidities. Secondary aims were to explore whether (1) use of nicotine

replacement therapy (NRT) during hospitalization was associated with clinical outcomes and (2) whether associations between prehospitalization vaccination and COVID-19 outcomes differed according to smoking status.

Methods

Study Design

The COVID EHR Cohort at the University of Wisconsin (CEC-UW; ClinicalTrials.gov: NCT04506528) is a retrospective cohort study established in May 2020 with support from the National Cancer Institute. Health systems affiliated with Cancer Center Cessation Initiative[33] and other large health systems were invited to participate. Health systems provided selected EHR data from all of their COVID-19 patients across the data collection period (February 1, 2020–January 31, 2022). The 21 participating health care systems (see Supplementary Figures S1 and S2 for system locations and number of patients from each system) extracted EHR data (monthly, then quarterly) and transmitted them to the University of Wisconsin Center for Tobacco Research and Intervention (UW-CTRI) coordinating center for harmonization and merging. The CEC-UW study was approved by the University of Wisconsin-Madison Health Sciences Minimal Risk Institutional Review Board (MR-IRB) for the collection of de-identified EHR data from the 21 health systems. The MR-IRB also determined that the study met criteria for a human subjects research exemption and qualified for a waiver of informed consent under the Federal Common Rule. All participating health systems provided written notice of either their own institution's IRB approval or determination of exemption status before sharing EHR data.

Cohort Definition

The analysis sample for this study focused on 104 590 patients hospitalized at the 21 health systems with COVID-19 between February 1, 2020 and September 30, 2021. Participants in this analysis had to (1) be age 18 or older, (2) be hospitalized for COVID-19 for at least 24 hours, or have died within 24 hours of admission or been transferred to the ICU within 24 hours of admission, (3) have a positive COVID-19 PCR test in a 14-day window from 7 days prior to admission to 7 days following admission or have an ICD-10 COVID-19 diagnosis during their hospitalization, and (4) have had prior contact with the admitting healthcare system. This last criterion increased data availability regarding comorbidities. Most patients had both a positive COVID-19 PCR test and an ICD-10 COVID-19 diagnosis (N = 76 303, 73.0%; 95% CI, 72.7–73.2). The remainder had a positive PCR test without an ICD-10 diagnosis (N = 7118, 6.8%, 95% CI, 6.7–7.0), a negative PCR test and an ICD-10 diagnosis (N = 10 115, 9.7%; 95% CI, 9.4–9.9), or no PCR test result and an ICD-10 diagnosis (N = 11 054, 10.6%; 95% CI, 10.4–10.8).

EHR Data Extraction

Customized data extraction code was developed by a team of programmers and consultants at UW Health (Madison, WI), Yale New Haven Health (New Haven, CT), and Bluetree Network, Inc. (Madison, WI). Extraction code targeted approximately 250 discrete EHR elements including sociodemographic data and basic health information, pre- and post-COVID-19 ICD-10 diagnoses, clinical encounter data, lab tests and results, and medication information. Each data extraction was retrospective to February 1, 2020 and captured new patients entering the cohort and follow-up data from patients identified at earlier extractions.

Primary and Secondary Outcomes

Mortality is the primary outcome, reflecting whether the patient died during the index hospitalization or was discharged alive. ICU admission is the secondary outcome and indicates whether the patient was admitted to intensive care. Data from hospitalized patients with undetermined outcome status at the time of the data extraction were not analyzed.

Smoking Status

Patient smoking status at the time of hospital admission was typically documented in the social history section of the EHR and was classified as never smoker, current smoker, former smoker, and missing (see Supplementary Table S1). The most recently recorded smoking status at the time of data extraction was used to classify patients.

Nicotine Replacement Therapy

Health systems provided information about medications prescribed during the hospitalization via RxNorm codes[34] and medication names. These data and their links to patient encounters yielded a binary variable indicating whether a patient was prescribed NRT during the index hospitalization.

Vaccination

Records indicating date and occurrence of COVID-19 vaccinations yielded a binary variable indicating patient receipt of at least one vaccine dose prior to the index hospital admission date.

Other Measures

Variables used as covariates and in descriptive analyses were sex, age, race, ethnicity, BMI, insurance status, and comorbid diagnoses. The levels of these categorical variables are given in Table 1. Comorbid diagnoses (present vs absent) were synthesized via a weighted Elixhauser comorbidity score for 5 years prior to the index hospitalization.[35] A 5-year lookback was selected because this identifies more comorbid conditions and yields equal or better prediction of clinical outcomes than shorter lookbacks.[36] Race and ethnicity categories were based on definitions used by the National Institutes of Health.[37]

Data Analysis

Relationships between smoking status and hospital outcomes were analyzed using generalized linear mixed model (GLMM) logistic regressions incorporating random intercepts to account for the clustering of patients within health systems.[38] For each outcome, separate models tested unadjusted associations with smoking status and adjusted associations accounting for patient covariates (age, sex, race, ethnicity, insurance status, BMI, and comorbidity). There were limited missing data for the outcome measures; one case with a missing value for ICU admission was omitted from analyses of this outcome. Patients with missing values on covariates were included in most statistical models using categories indicating missingness where needed (see Table 1).

The association between NRT use and each of the hospital outcomes was tested in separate GLMM models, limited to current smokers, with and without adjustment for the covariates used in the main outcome analyses.

Table 1. Demographic characteristics of the CEC-UW COVID-19 inpatients ages 18 and older, overall and by smoking status.

Characteristic	Total *N* (%)	Never smoker *N* (%)	Current smoker *N* (%)	Former smoker *N* (%)	Missing status *N* (%)	Cramer's *V*
Full sample	104 590 (100)	57 454 (54.9)	7764 (7.4)	33 101 (31.6)	6271 (6.0)	
Sex						.102
Female	52 701 (50.4)	32 644 (56.8)[a]	3043 (39.2)[b]	14 092 (42.6)[c]	2922 (46.6)[d]	
Male	51 887 (49.6)	24 809 (43.2)[a]	4721 (60.8)[b]	19 008 (57.4)[c]	3349 (53.4)[d]	
Other	2 (0.0)	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	
Age						.148
18–29	6360 (6.1)	4779 (8.3)[a]	556 (7.2)[b]	652 (2.0)[c]	373 (5.9)[d]	
30–39	8528 (8.2)	5692 (9.9)[a]	1035 (13.3)[b]	1328 (4.0)[c]	473(7.5)[d]	
40–49	10 602 (10.1)	6859 (11.9)[a]	1092 (14.1)[b]	2036 (6.2)[c]	615 (9.8)[d]	
50–64	29 032 (27.8)	16 329 (28.4)[a]	2787 (35.9)[b]	8324 (25.1)[c]	1592 (25.4)[c]	
65–74	21 795 (20.8)	10 313 (18.0)[a]	1471 (18.9)[b]	8827 (26.7)[c]	1184 (18.9)[a,b]	
75–84	17 428 (16.7)	7870 (13.7)[a]	658 (8.5)[b]	7846 (23.7)[c]	1054 (16.8)[d]	
85+	10 845 (10.4)	5612(9.8)[a]	165 (2.1)[b]	4088 (12.4)[c]	980(15.6)[d]	
Race						.096
American Indian or Alaska Native	389 (0.4)	221 (0.4)[a]	32 (0.4)[a,b]	122 (0.4)[a,b]	14 (0.2)[b]	
Asian	3047 (2.9)	2097 (3.6)[a]	93 (1.2)[b]	614 (1.9)[c]	243 (3.9)[a]	
Black or African American	25073 (24.0)	13 285 (23.1)[a]	2826 (36.4)[b]	7210 (21.8)[c]	1752 (27.9)[d]	
Native Hawaiian or Pacific Islander	484 (0.5)	333 (0.6)[a]	20 (0.3)[b]	96 (0.3)[b]	35 (0.6)[a]	
White	59 362 (56.8)	30 852 (53.7)[a]	3929 (50.6)[b]	21 646 (65.4)[c]	2935 (46.8)[d]	
Other or Not Specified	14 116 (13.5)	9404 (16.4)[a]	739 (9.5)[b]	2925 (8.8)[b]	1048 (16.7)[a]	
More than one	366 (0.3)	186 (0.3)[a]	32 (0.4)[a,b]	110 (0.3)[a]	38 (0.6)[b]	
Missing	1753 (1.7)	1076 (1.9)[a]	93 (1.2)[b]	378 (1.1)[b]	206 (3.3)[c]	
Ethnicity						.093
Hispanic or Latino	16 661 (15.9)	11 292 (19.7)[a]	770 (9.9)[b]	3508 (10.6)[b]	1091 (17.4)[c]	
Not Hispanic or Latino	84 827 (81.1)	44 355 (77.2)[a]	6792 (87.5)[b]	28 858 (87.2)[b]	4822 (76.9)[a]	
Missing	3102 (3.0)	1807 (3.1)[a]	202 (2.6)[b]	735 (2.2)[c]	358 (5.7)[d]	
Body mass index						.081
Underweight	3042 (2.9)	1371 (2.4)[a]	404 (5.2)[b]	993 (3.0)[c]	274 (4.4)[b]	
Healthy weight	23 483 (22.5)	11 839 (20.6)[a]	2340 (30.1)[b]	7674 (23.2)[c]	1630 (26.0)[d]	
Overweight	29 940 (28.6)	16 390 (28.5)[a]	2094 (27.0)[b]	9748 (29.4)[c]	1708 (27.2)[b]	
Obese	35 095 (33.6)	20 128 (35.0)[a]	2135 (27.5)[b]	11 053 (33.4)[c]	1779 (28.4)[b]	
Severely obese	11 997 (11.5)	7234 (12.6)[a]	733 (9.4)[b]	3465 (10.5)[c]	565 (9.0)[b]	
Missing or biologically implausible	1033 (1.0)	492 (0.9)[a]	58 (0.7)[a]	168 (0.5)[b]	315 (5.0)[c]	
Insurance status						.141
Medicare	55 427 (53.0)	26 636 (46.4)[a]	3092 (39.8)[b]	22 373 (67.6)[c]	3326 (53.0)[d]	
Medicaid	12 177 (11.6)	6481 (11.3)[a]	1987 (25.6)[b]	2751 (8.3)[c]	958 (15.3)[d]	
Commercial	27 921 (26.7)	18 948 (33.0)[a]	1600 (20.6)[b]	5984 (18.1)[c]	1389 (22.1)[d]	
Uninsured	1967 (1.9)	1127 (2.0)[a]	266 (3.4)[b]	392 (1.2)[c]	182 (2.9)[b]	
Other	7098 (6.8)	4262 (7.4)[a]	819 (10.5)[b]	1601 (4.8)[c]	416 (6.6)[d]	
Elixhauser Comorbidity Index						—
M (*SD*)[e]	5.45 (9.49)	4.44 (8.56)[a]	5.15 (9.89)[b]	7.97 (10.84)[c]	1.77 (5.55)[d]	

Proportions in the same row not sharing the same superscript differ significantly at $p < .05$. All Cramer's *V* values $p < .001$.
[e]Pairwise comparisons reflect group differences in distribution using nonparametric Kruskal–Wallis analysis.

A final set of unadjusted and adjusted models tested whether smoking status moderated associations between vaccination status and hospital outcomes. These analyses were limited to hospitalizations occurring on or after December 11, 2020, when the US Food and Drug Administration (FDA) issued the first COVID-19 vaccine emergency use authorization.[39]

Results

Descriptive Findings

Of the 104 590 hospitalized patients, 57 454 (54.9%; 95% CI, 54.6–55.2) were never smokers, 7764 (7.4%; 95% CI, 7.3–7.6) were current smokers, 33 101 (31.6%; 95% CI, 31.4–31.9) were former smokers, and 6271 (6.0%; 95%

Table 2. Associations of Smoking Status With Hospital Outcomes (N = 104 590)

	Outcome	Unadjusted			Adjusted[a]		
	Mortality ***n*** **died (%, 95% CI)**	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Never smoker (Ref)	4800 (8.4, 8.1–8.6)	1.00	—	—	1.00	—	—
Current smoker	529 (6.8, 6.3–7.4)	0.84	0.76, 0.92	<.001	0.98	0.89, 1.08	.662
Former smoker	3953 (11.9, 11.6–12.3)	1.57	1.50, 1.64	<.001	1.11	1.06, 1.17	<.001
Missing smoking status	971 (15.5, 14.6–16.4)	1.87	1.73, 2.02	<.001	1.71	1.57, 1.85	<.001
	ICU admission ***n*** **admitted (%, 95% CI)**	**OR**	**95% CI**	***p***	**OR**	**95% CI**	**p**
Never smoker (Ref)	10 668 (18.6, 18.3–18.9)	1.00	—	—	1.00	—	—
Current smoker	1599 (20.6, 19.7–21.5)	1.06	1.00[b], 1.13	.049	1.00	0.94, 1.07	.930
Former smoker	7426 (22.4, 22.0–22.9)	1.23	1.19, 1.27	<.001	1.07	1.04, 1.11	<.001
Missing Smoking Status	1615 (25.8, 24.7–26.9)	1.77	1.66, 1.88	<.001	1.77	1.66, 1.89	<.001

CI, confidence interval; Ref, reference category; OR, odds ratio.
[a]Adjusted for sex, age, race, ethnicity, insurance status, BMI, and past 5-year comorbidity score. Full results from adjusted models are presented in Supplementary Tables S3 and S4.
[b]Lower bound = 1.0003.

CI, 5.9–6.1) were missing smoking status information. Table 1 presents patient characteristics for the sample as a whole and by smoking status. Of the categorical variables, smoking status was most strongly associated with age and insurance status. Relative to never smokers, current smokers tended to be younger and former smokers tended to be older. Consistent with these age effects, Medicare (a US government insurance program for persons 65 and older and persons under 65 with disabilities) was less common among current smokers and more common among former smokers. Rates of Medicaid (a US government insurance program for persons with low income) and being uninsured were highest among current smokers. Comorbidity scores were highest among former smokers, followed by current smokers, never smokers, and lowest in those missing smoking status. Supplementary Table S2 presents results from a multivariate analysis predicting missing smoking status.

Overall, 10 253 (9.8%; 95% CI, 9.6–10.0) patients died in hospital and 21 308 (20.4%; 95% CI, 20.1–20.6) patients were admitted to ICU. ICU admission was associated with mortality (OR, 10.46, 95% CI, 9.97–10.96, p < .001). More than half of the patients who died (59.8%, 95% CI, 58.8–60.8, n = 6132) were admitted to ICU compared with just 16.1% (95% CI, 15.9–16.3, n = 15 176) of patients who did not die.

Smoking Status and Hospital Outcomes

Table 2 summarizes results from unadjusted and adjusted models testing associations between smoking status and hospital outcomes. Full results from the adjusted models are provided in Supplementary Tables S3 and S4. Adjusted odds of death did not differ in current smokers compared to never smokers (aOR, 0.98; 95% CI, 0.89–1.08, p = .662). Former smokers (aOR, 1.11; 95% CI, 1.06–1.17, p <.001) and patients with missing smoking status (aOR, 1.71; 95% CI, 1.57–1.85, p <.001) were significantly more likely to die compared to never smokers.

Relative to never smokers, adjusted odds of ICU admission did not differ for current smokers (aOR, 1.00; 95% CI, 0.94–1.07, p = .930) but were significantly higher among former smokers (aOR, 1.07; 95% CI, 1.04–1.11, p <.001) and those missing smoking status (aOR, 1.77; 95% CI, 1.66–1.89, p <.001).

Nicotine Replacement Therapy

A total of 2124 current smokers (27.4%; 95% CI, 26.4–28.4) were prescribed NRT, primarily transdermal patches (Supplementary Table S5), during the index hospitalization. Supplementary Table S6 shows demographic characteristics of NRT recipients, and Supplementary Table S7 summarizes a multivariate analysis predicting NRT prescription.

Of 2124 current smokers prescribed NRT, 95 died (4.5%; 95% CI, 3.7–5.5) compared to 434 (7.7%; 95% CI, 7.0–8.4) of the 5640 current smokers without a documented NRT prescription. NRT was associated with reduced adjusted odds of mortality (aOR, 0.64; 95% CI, 0.50–0.82, p <.001; Supplementary Table S8). This effect remained after further adjustment for ICU admission (aOR, 0.57; 95% CI, 0.44–0.74, p <.001; Supplementary Table S9). Current smokers' ICU admission rate was 21.6% (95% CI, 19.8–23.4; n = 458) when prescribed NRT vs. 20.2% when not NRT (95% CI, 19.2–21.3; n = 1141). NRT was not associated with ICU admission (aOR, 1.04; 95% CI, 0.91–1.19, p = .607; Supplementary Table S10).

Vaccination Status

In the subsample of 54 983 patients hospitalized on or after the first FDA COVID-19 vaccine emergency use authorization, 6344 (11.5%, 95% CI, 11.3–11.8) had a documented history of receiving at least one vaccine dose prior to admission. Supplementary Tables S11–S13 summarize the patterns of specific vaccines recorded, demographic characteristics by vaccination status, and results from a multivariate model predicting vaccination status.

A total of 369 (5.8%; 95% CI, 5.3–6.4) vaccinated patients died compared to 3961 (8.1%; 95% CI, 7.9–8.4) of those without an EHR-documented prehospitalization vaccination

(aOR, 0.55; 95% CI, 0.49–0.61, p <.001). Similarly, fewer vaccinated patients were admitted to the ICU (16.9%; 95% CI, 15.9–17.8, n = 1069) than patients without a documented vaccination history (18.7%; 95% CI, 18.3–19.0, n = 9080), a significant difference (aOR, 0.80; 95% CI, 0.74–0.86, p < .001).

Figure 1A presents observed mortality rates by smoking and vaccination status (data presented in tabular form in Supplementary Table S14). Smoking status significantly moderated associations between vaccination status and both mortality and ICU admission in unadjusted and covariate-adjusted models (Supplementary Tables S15–S17). These interactions were probed with stratified logistic analyses (Table 3). In covariate-adjusted analyses stratified by smoking group, vaccination (vs no recorded vaccination) was associated with significantly lower odds of death in never smokers (aOR, 0.67; 95% CI, 0.57–0.79, p < .001), current smokers (aOR, 0.29; 95% CI, 0.16–0.55, p <.001), and former smokers (aOR, 0.47; 95% CI, 0.39–0.56, p < .001), but not those with missing smoking status (aOR, 0.60; 95% CI, 0.35–1.04, p = .066). Specific interaction contrasts (Supplementary Table S15) indicated that, relative to the effect in never smokers, vaccination's association with reduced mortality was significantly more pronounced among current smokers (current × vaccine aOR, 0.46; 95% CI, 0.24–0.86, p = .015) and former smokers (former × vaccine aOR, 0.70; 95% CI, 0.56–0.90, p = .003), but not in patients with missing smoking status (missing × vaccine aOR, 0.85; 95% CI, 0.48–1.48, p = .557).

Figure 1B shows observed ICU admission rates by smoking and vaccination status (see also Supplementary Table S14). In covariate-adjusted analyses stratified by smoking group (see Table 3), vaccination was associated with significantly reduced odds of ICU admission among never smokers (aOR, 0.87; 95% CI, 0.79–0.97, p = .010), current smokers (aOR, 0.73; 95% CI, 0.55–0.96, p = .025), and former smokers (aOR, 0.74; 95% CI, 0.66–0.83, p < .001). The effect of vaccination was not significant in patients with missing smoking information (aOR, 0.78; 95% CI, 0.53–1.16, p = .220). Interaction contrasts (Supplementary Table S15) indicated that the reduction in risk of ICU admission associated with vaccination was significantly more pronounced among former smokers than in never smokers (former × vaccine aOR, 0.82; 95% CI, 0.70–0.96, p = .011). The association between vaccination and ICU admission did not differ in current smokers (current × vaccine aOR, 0.78; 95% CI, 0.58–1.04, p = .085) or in patients with missing smoking status (missing × vaccine aOR, 0.86; 95% CI, 0.58–1.28, p = .462) relative to the association in never smokers.

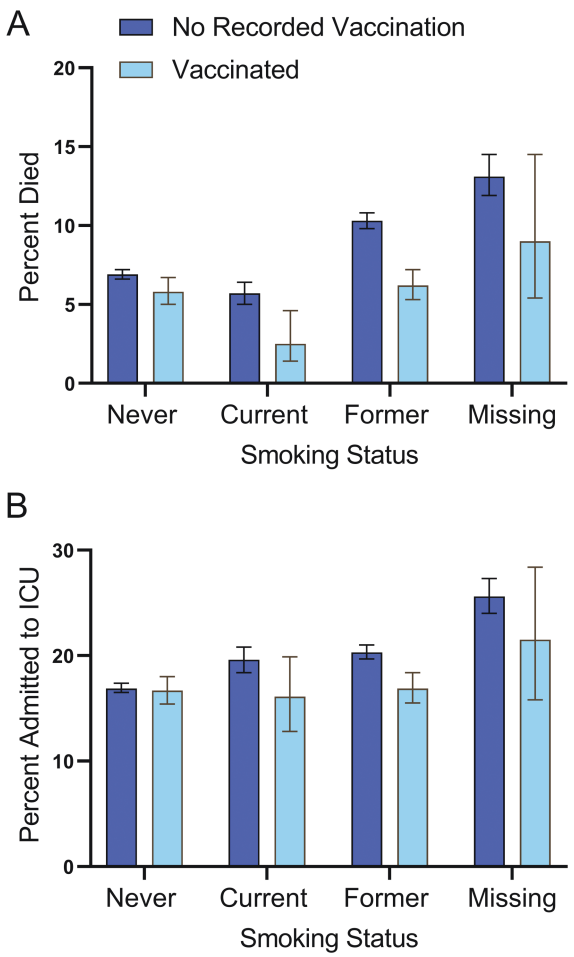

Figure 1. (A) Observed mortality rates and associated 95% confidence intervals by smoking status and vaccination status. (B) Observed ICU admission rates and associated 95% confidence intervals by smoking status and vaccination status.

Sensitivity Analyses

Sensitivity analyses were conducted to evaluate robustness of the findings. Smoking status was determined using the most recent EHR entry available at the time of the final data pull. Supplementary Tables S18–S23 show that the results are little changed by restricting the analyses to participants for whom smoking status was documented in the interval from 31 days before admission to 7 days after admission. A notable difference was that the adjusted NRT effect on mortality was somewhat reduced and no longer significant in this smaller sample (aOR = 0.78; 95% CI, 0.57–1.06, p = .110).

For some patients classified as current smokers, NRT in-hospital may have been prescribed to support continuation of an ongoing quit attempt, calling into question their true smoking status on admission. Associations between NRT and hospital outcomes were unchanged when eliminating patients who had any documented past-year prehospitalization NRT prescription (Supplementary Tables S24 and S25).

When vaccination status was represented with a three-level categorical variable (none documented, partially vaccinated, and fully vaccinated, defined as hospitalization ≥ 14 day beyond the last dose of the indicated sequence), the omnibus interaction between vaccination and smoking status remained significant when predicting mortality but not ICU admission (Supplementary Tables S26–S29). Effect size estimates were generally comparable to those from binary vaccination models but confidence intervals around specific interaction estimates were wider and p-values were more variable when splitting out vaccine subgroups.

Data were collected over a 15-month period during which there were shifts in the prevailing SARS-CoV-2 variants, treatment protocols, and vaccine availability. To explore whether associations with smoking status and hospital outcomes varied over time we divided the data into two periods (February 2020–June 2020 and July 2020–September 2021) based on

Table 3. Results from stratified logistic analyses probing smoking status x vaccination status interactions. (*N* = 54 983)

Outcome/ Model	Unadjusted			Adjusted[a]		
	OR	95% CI	*p*	OR	95% CI	*p*
Mortality						
Stratified by smoking status						
Never smoker						
Vaccination (vs none)[b]	0.90	0.77, 1.05	.190	0.67	0.57, 0.79	<.001
Current smoker						
Vaccination (vs none)	0.43	0.23, 0.79	.007	0.29	0.16, 0.55	<.001
Former smoker						
Vaccination (vs none)	0.60	0.51, 0.71	<.001	0.47	0.39, 0.56	<.001
Missing smoking status						
Vaccination (vs none)	0.69	0.41, 1.17	.171	0.60	0.35, 1.04	.066
Stratified by vaccination						
No recorded vaccination						
Never smoker (Ref)	1.00	—	—	1.00	—	—
Current smoker	0.83	0.72, 0.95	.008	0.98	0.85, 1.13	.739
Former smoker	1.59	1.48, 1.71	<.001	1.12	1.04, 1.21	.003
Missing smoking status	2.03	1.79, 2.30	<.001	1.90	1.67, 2.16	<.001
Vaccinated						
Never smoker (Ref)	1.00	—	—	1.00	—	—
Current smoker	0.41	0.22, 0.76	.005	0.40	0.21, 0.75	.004
Former smoker	1.06	0.85, 1.32	.585	0.79	0.63, 1.00	.051
Missing smoking status	1.56	0.91, 2.68	.105	1.56	0.89, 2.74	.122
ICU admission						
Stratified by smoking status						
Never smoker						
Vaccination (vs none)	0.95	0.85, 1.05	.270	0.87	0.79, 0.97	.010
Current smoker						
Vaccination (vs none)	0.80	0.61, 1.05	.108	0.73	0.55, 0.96	.025
Former smoker						
Vaccination (vs none)	0.77	0.69, 0.86	<.001	0.74	0.66, 0.83	<.001
Missing smoking status						
Vaccination (vs none)	0.80	0.55, 1.18	.262	0.78	0.53, 1.16	.220
Stratified by vaccination						
No recorded vaccination						
Never smoker (Ref)	1.00	—	—	1.00	—	—
Current smoker	1.12	1.03, 1.22	.008	1.09	1.00, 1.19	.052
Former smoker	1.23	1.17, 1.30	<.001	1.08	1.02, 1.14	.005
Missing smoking status	1.91	1.74, 2.10	<.001	1.93	1.75, 2.13	<.001
Vaccinated						
Never smoker (Ref)	1.00	—	—	1.00	—	—
Current smoker	0.92	0.70, 1.21	.559	0.80	0.60, 1.07	.132
Former smoker	1.00	0.87, 1.15	.992	0.91	0.78, 1.05	.189
Missing smoking status	1.65	1.13, 2.42	.010	1.62	1.10, 2.39	.016

CI, confidence interval; Ref, reference category; OR, odds ratio.
[a]Adjusted for sex, age, race, ethnicity, insurance status, BMI, and past 5-year comorbidity score.
[b]Comparison of patients with a prehospitalization EHR-documented vaccine dose to those with no EHR record of vaccination.
Omnibus interaction effects from models including interaction terms (Supplementary Tables S15–S17):
Smoking Status × Vaccine interaction for mortality, unadjusted F (3, 54 975) = 4.84, p = .002;
Smoking Status × Vaccine interaction for mortality, adjusted F (3, 54 949) = 4.16, p = .006.
Smoking Status × Vaccine interaction for ICU admission, unadjusted F (3, 54 975) = 2.68, p = .045.
Smoking Status × Vaccine interaction for ICU admission, adjusted F (3, 54 949) = 2.64, p = .048.

an inflection point the overall rate of in-hospital mortality, which was highest early in the pandemic (Supplementary Figure S3). Period significantly moderated the associations of mortality and ICU admission with smoking status (Supplementary Tables S30 and S31). This effect was driven by stronger associations between missing smoking status and outcomes in the later period compared to the initial months of the pandemic.

Table 3. Continued

Discussion

Findings from this large, multisite cohort study indicated that there were few differences between current smokers and never smokers with respect to key COVID-19 hospital outcomes (death and ICU admission). In unadjusted models, current (vs never) smoking was associated with lower mortality and increased risk of admission to intensive care. However, these effects were eliminated after adjustment for other patient characteristics. The lack of association between current smoking and COVID-19 outcomes is surprising given the well-known adverse effects of smoking on the respiratory system including increased susceptibility to respiratory infections.[2,3] Meta-analytic reviews have identified substantial heterogeneity of effect sizes when evaluating associations between current smoking and progression to serious COVID-19 disease and have reached discrepant conclusions with respect to the statistical significance of pooled effects.[11,19,20,23,24] Our findings add to a complicated literature indicating that (1) current smoking per se is not consistently predictive of COVID-19 severity and (2) observed effects of current smoking in unadjusted models may be accounted for by other patient characteristics that differ between current and never smokers.

In contrast, former smoking was consistently associated with poorer hospital outcomes relative to never smoking. Former smokers were older and sicker than never smokers and current smokers (Table 1) consistent with the notion that smoking-related disease may ultimately promote smoking cessation[40] and attempts over many years are needed to quit successfully.[41] Statistical adjustment for multiple covariates (including age and comorbidity) attenuated but did not eliminate associations of former (vs. never) smoking with mortality and ICU admission. Of course, covariates likely did not equate these groups for all COVID-19 risks other than smoking history.

Patients with missing smoking status had the worst hospital outcomes in this cohort. These findings are consistent with those of some other cohort studies[29,30] but are difficult to explain. These patients were not historically sicker than those with documented smoking status—in fact, pre-COVID-19 comorbidity scores tended to be lowest among patients with missing smoking status (Table 1). It does not appear that their missing data occurred because they were new to the health system; ~75% had at least two prior health system encounters. Future research is needed to explain the association between missing smoking status in the EHR and COVID-19 disease severity.

Among current smokers, NRT prescription was associated with reduced mortality. Several hypotheses have been forwarded regarding a possible mitigating effect of nicotine on COVID-19 outcomes, with these involving nicotine activating various anti-inflammatory mechanisms.[12,13,42–46] It is important to note that the current, observational findings cannot establish a causal effect of NRT. An alternative explanation may be that patients with less severe acute illness were more likely to receive NRT. Medical management of uncomfortable tobacco withdrawal symptoms may simply be most likely when patients are in a more stable condition and able to communicate with the treatment team. Two clinical trials investigating the efficacy of nicotine replacement therapy among individuals hospitalized with COVID-19 have been completed but their results have not yet been reported (ClinicalTrials.gov NCT04608201, NCT04598594).

Prior vaccination for COVID-19 was protective against death in this cohort, and this effect was accentuated among current and former smokers relative to never smokers. Among vaccinated patients, current smokers had the lowest mortality rate and former smokers and never smokers had comparable rates. Similarly, vaccination was associated with reduced need for intensive care, and the incremental benefit was larger in former smokers relative to never smokers. These findings are surprising given evidence of reduced serological response to COVID-19 vaccines in smokers.[32] If these findings are replicable, messaging concerning the enhanced benefits of vaccination among current and former smokers might be useful for addressing vaccine hesitancy in these groups.[31]

Several limitations should be considered when interpreting these findings. Sample sizes of the smoking groups differed substantially; interpretation of the findings should consider statistical power and absolute effect sizes. Smoking status as collected in the EHR often does not capture important characteristics of tobacco use history (eg, heaviness of current use, pack-years of exposure, years since quitting) that may yield additional evidence regarding COVID-19 outcomes. The accuracy of smoking status records in this sample is unknown, but prior research suggests EHR smoking status information is frequently incorrect or internally discrepant.[47] Missing smoking status was a major predictor of severe disease outcomes. Risk estimates associated with current or former smoking could be biased if individuals belonging to these categories were disproportionately represented in the missing group. Analyses of vaccine effects contrasted individuals with a documented history of prehospital vaccination to those without such documentation. This comparison group may have included patients who received vaccine doses that were not recorded in the EHR. A similar caveat applies to the reference group in the NRT comparison. Only data from discrete fields in the EHR were extracted; it is likely some information on smoking status, NRT, and vaccination status was missed by not extracting and algorithmically searching free text fields. Data were available on NRT prescriptions only rather than actual use. Additionally, the analyses did not consider variations in dose or formulation of NRT or differing types of vaccines. The interactive effects of smoking status and vaccination were robust to adjustment for patient characteristics, many of which were predictive of vaccination status (Supplementary Table S13). However, we cannot rule out residual confounding by unmeasured factors. Selection bias occurring on the contingent pathway from vaccination to infection to hospitalization could also play a role. Because medical comorbidity is an important predictor of COVID-19 outcomes, we limited analyses to patients with prior contact with the health care system for whom historical data permitted identification of preexisting conditions. This criterion eliminated over 25 000 hospitalizations and the excluded patients differed from the analytic sample on numerous patient characteristics (Supplementary Table S32). Temporal and geographic variation in circulating viral variants affects rates of hospitalization, severity of COVID-19 illness, and vaccine effectiveness.[48] More work is needed to investigate whether and how these factors moderate the effects reported here. Additional research is also needed to evaluate the generalizability of the findings to other countries. Finally, results were available only for the participating health systems, no post-discharge outcomes were examined, and data from nonhospitalized patients were not analyzed.

In summary, analyses from this large EHR cohort found that former smokers hospitalized with COVID-19 were more likely than never smokers to be admitted to intensive care and to die, effects that were reduced but not eliminated when accounting for age, medical comorbidities, and other patient factors. In contrast, current smokers with COVID-19 did not differ from never smokers in ICU admission and death when statistically adjusting for covariates. Hospitalized COVID-19 patients with missing smoking status information had the worst outcomes overall. In current smokers, NRT prescription during the hospitalization was associated with decreased mortality. Finally, COVID-19 vaccination was associated with especially large decreases in mortality among current and former smokers versus never smokers. Additional research is needed to explore the mechanisms underlying these associations.

Supplementary Material

A Contributorship Form detailing each author's specific involvement with this content, as well as any supplementary data, are available online at https://academic.oup.com/ntr.

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Declaration of Interests

None declared.

Data Availability

The existing Data Transfer and Use Agreements negotiated with each of the 21 participating health systems preclude the University of Wisconsin from sharing these data with any entity at this time. Information Management Services, Inc. (IMS), under contract from the National Cancer Institute (NCI) is responsible for housing the final CEC-UW data. A small number of health systems have put limits on the extent of data sharing. Data from most health systems will eventually be made available to approved researchers, who are to be determined by NCI and/or IMS.

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